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Hypertensive disorders during pregnancy and offspring retinal microvasculature during adolescence

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Offspring of mothers with hypertensive disorders during pregnancy (HDP) have increased risk of cardiovascular disease (CVD) (1). Whether this is due to a direct *intra uterine* effect, such as maternal inflammation, endothelial dysfunction or poor placentation linked pre-eclampsia (PE), or shared genetics or environment, which is more likely to be linked to gestational hypertension (GH), remains undetermined (1). Regardless, it is proposed that microvascular changes that predate CVD events by decades could play a role (2). Retinal scans are a non-invasive way to directly observe the human microvasculature. We therefore examined whether exposure to maternal HDP was associated with retinal microvascular features in adolescent offspring in a UK pregnancy cohort.

We included 1,082 singletons with information on maternal HDP and retinal microvasculature at age 13 from the Avon Longitudinal Study of Parents and Children (ALSPAC). Ethical approval was granted by the ALSPAC Law and Ethics Committee and local research ethics committees. Women without pre-existing hypertension were classified with gestational hypertension (GH) if they had systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least 2 occasions first occurring after 20 gestational weeks. Pre-eclampsia (PE) was defined as GH in combination with proteinuria (≥ 30g/dL). We compared children of mothers with GH and PE to children of mothers without pre-existing hypertension. Measures of retinal microvasculature included arteriolar diameters, venular diameters, arteriolar length diameter ratio, arteriolar tortuosity, arteriovenous ratio and optimality deviance. The multivariable linear regression models adjusted for sex, age at retinal scans, and ametropia (Model 1), in addition to maternal age, parity, education, pre-pregnancy BMI, smoking and grandparental history of CVD (Model 2).

A total of 159 mothers (15%) had GH, while 18 (2%) had PE. The mean age of the children at the time of the retinal scans was 12.8 years (standard deviation 0.2). Maternal GH showed modest associations with offspring retinal venular diameter, adjusted mean difference

2.62 microns (95% CI: 0.26, 4.98), and arteriovenous ratio, adjusted mean difference -0.02 (95% CI: -0.04, -0.01) (Table). Similar associations were not observed for PE, with an adjusted mean difference of 0.94 microns (95% CI: -5.50, 7.38) for retinal venular diameter, and an adjusted mean difference of -0.01 (95% CI: -0.05, 0.04) for arteriovenous ratio (Table). There was no strong evidence of any additional associations. Excluding children with childhood-onset diabetes (N=3), did not change results.

Our findings indicate that children born to mothers with GH (but not PE) have a greater venular diameter and a lower arteriovenous ratio. In contrast to findings from the Generation R cohort which examined children at age six, our findings do not support a narrower arteriolar diameter among children exposed to HDP (3). The differences between our findings and those from Generation R may be explained by the fact that they measured retinal microvasculature at age 6 instead of age 13, or the fact that they did not separate GH from PE, as they grouped both conditions into HDP. However, both narrower arterioles and wider venules are known to predict future hypertension and CVD events (4). It is therefore plausible that there might be a microvascular pathway linking HDP and increased CVD risk in offspring (4). The associations of maternal GH - but not of PE - with offspring cardiovascular health are also in line with associations previously reported for offspring blood pressure in ALSPAC (5). A potential explanation may be that GH is more likely driven by underlying genetic predisposition and lifestyle characteristics, whilst PE is driven by a specific pregnancy profile, e.g. placentation. In conclusion, our results indicate that children of mothers with GH have a wider venular diameter and lower arteriovenous ratio. This might be explained by a common role of genetic or lifestyle characteristics linked to CVD risk.

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Table The mean difference in measures of retinal microvasculature between offspring of mothers with hypertensive disorders during pregnancy and offspring of normotensive mothers
(n=1,082)

Measure of microvasculature	Gestational hypertension Mean difference (95% CI)	Pre-eclampsia Mean difference (95% CI)	Direction of the association between the microvascular measures and later cardiovascular risk
Arteriolar diameter, microns			↓
Model 1	0.19 (-1.60, 1.98)	0.42 (-4.52, 5.35)	
Model 2	0.27 (-1.57, 2.12)	0.93 (-4.10, 5.97)	
Venular diameter, microns			↑
Model 1	3.08 (0.78, 5.37)	1.25 (-5.08, 5.57)	
Model 2	2.62 (0.26, 4.98)	0.94 (-5.50, 7.38)	
Arteriolar length diameter ratio (LDR)			↑
Model 1	-0.37 (-0.93, 0.19)	-0.83 (-2.37, 0.72)	
Model 2	-0.39 (-0.97, 0.18)	-0.95 (-2.53, 0.62)	
Arteriolar tortuosity			↓
Model 1	-0.002 (-0.006, 0.002)	-0.004 (-0.015, 0.007)	
Model 2	-0.001 (-0.006, 0.003)	-0.003 (-0.014, 0.009)	
Arteriovenous ratio			↓
Model 1	-0.03 (-0.04, -0.01)	-0.01 (-0.06, 0.03)	
Model 2	-0.02 (-0.04, -0.01)	-0.01 (-0.05, 0.04)	
Optimality deviance[a]			↑
Model 1	-0.002 (-0.017, 0.012)	0.009 (-0.032, 0.050)	
Model 2	-0.003 (-0.019, 0.013)	0.008 (-0.034, 0.049)	

CI=confidence interval.

Model 1 Adjusted for age, sex and ametropia.

Model 2 Adjusted for age sex and ametropia, in addition to maternal age, parity, education, pre-pregnancy BMI, smoking during pregnancy and genetic predisposition to cardiovascular disease (parental history of hypertension, stroke or heart disease).

[a] For a theoretically optimal bifurcation, the optimality ratio should be 0.79, and the optimality deviance was calculated as the absolute value of the optimality ratio minus 0.79.

Multiple imputation of missing covariate information conducted using chained equations.